REMARKS

Claims 11-18, 29 and 30 have been withdrawn from consideration and all other pending claims (*i.e.*, claims 22-25) have been rejected. The Examiner has acknowledged a priority claim to application 09/226,012, filed June 6, 1999. The Examiner has also acknowledged a claim to priority to U.S. Application No. 122,847 filed July 27, 1998 (the '847 application), but has granted priority to this date only with respect to claims which recite the specific mutations Cys 572, Asp 588 and Ala 630. Applicants note that the additional mutation of V614 was disclosed at page 75, line 28 of the '847 application. By this amendment, claims 11-18, 29 and 30 have been canceled without prejudice to refiling in one or more divisional or continuing applications and claims 22 and 23 have been amended. It is believed that the amendments do not constitute new matter and their entry is requested.

35 U.S.C. 112 enablement rejections

Claims 22-25 were rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner is of the opinion that the nature of the invention being examined is a method to screen for drugs useful in treating a person having one of the five mutations in HERG selected from the group consisting of Cys 572, Asp 588, Val, 614, Ala 630 and Leu 29. The method is acknowledged by the Examiner to comprise measuring induced K+ current in mutant versus wildtype HERG cells, adding a drug to the mutant cells and measuring K+ current, wherein restoration of levels found in wildtype HERG cells to mutant cells after addition indicates that a drug will be useful in treating patients with a mutation in HERG.

The Examiner has acknowledged that a 614V mutation results in loss of K+ function and that the claims are enabled for this specific mutation. It is the Examiner's opinion, however, that it is not known whether or not any of the other mutations encompassed by the claims would result in loss of HERG function or alteration in K+ channel conductivity. The essence of the enablement rejection appears to be that the Examiner is of the opinion that the art does not teach that the specific mutations 29L, 572C, 588D or 630A in the HERG gene cause LQT syndrome **or** loss of K+ function. Based on these observations, the Examiner is of the opinion that if it is unknown whether or not the other mutations produce a change in K+ function, than these embodiments are not enabled.

In response to the Examiner's rationale for the enablement rejections, Applicants submit that the Examiner has not provided any explanation as to why the cited mutations would not be expected to alter K+ channel conductivity and thus has not provided the specific technical reasons required to establish non-enablement. Furthermore, mutations in the amino acid residues encompassed by the claims do indeed result in an alteration of K+ conductivity. Nakajima et al. Circ. Res. 83:415-422 (1998); "Nakajima") clearly establishes that alteration of the 614 and 630 residues cause change in K+ channel activity. As noted by the Examiner, alteration of amino acid 614 to specifically valine causes a change in K+ channel activity. Additional references in the literature establish that alterations residue in residue 29 of HERG also result in alteration of K+ activation, both for F29L and F29A alterations (Chen et al. J. Biol Chem 274(15):10113-10118 (1999); and Morais Cabral et al. Cell 95: 649-655 (1998); copies attached). Also, a mutation in residue 572 of HERG has also been linked to symptoms associated with alteration of the K+ channel, *i.e.*, syncope, ventricular fibrillation and sudden death (Larsen et al. Clin. Genet 57:125-130 (2000); copy attached).

In sum, of the five mutations encompassed by the claims, all five have been linked to LQT syndrome, three of the targeted amino acid residues (29, 614 and 630) have been conclusively identified as altering K+ channel activity and a fourth (572) has been associated with physical symptoms associated with K+ channel activity. Furthermore. of the three amino acid residues conclusively identified as regulating K+ channel activity, two of the three specific mutations encompassed by the claims (29A and 614V) have been confirmed as altering K+ channel activity. With regard to the fifth residue encompassed by the claims (588), this amino acid position is located in the transmembrane portion subunit 5, which is directly adjacent to the K+ pore forming region and is also known to be involved in K+ channel formation (See Specification, Table 7; See also Wang et al. MOLECULAR MEDICINE TODAY:382-388 (1998) and Nakajima).

The present specification thus discloses five mutations in critical regions of HERG that are changed in persons afflicted with LQT (Table 7 and page 77, lines 5-8). All five locations in HERG have been shown to be integral in affecting K+ ion channel activation. It is respectfully submitted that, absent some specific technical reasoning as to why <u>any</u> of the specific mutations encompassed by the claims as amended would not be expected to impact K+ channel formation, the Examiner has not met the burden required under the patent statutes to establish non-enablement.

The pending claims were also rejected for lack of enablement as being too broad with respect to transgenic animals with loss of K+. The essence of this rejection is based on the reference Wall, *Theriogenology* 45:57-58 (1996) which is cited for the proposition that physiological consequences of transgene products are not predictable in mouse studies. Based on the foregoing, the Examiner is of the opinion that the production of transgenic animals with the claimed phenotype required for the claimed methods may or may not be possible to construct an therefore absent working examples, the claims are not enabled. In response, it is submitted that the only relevant claim to this objection is claim 25, which claims a method as in claim 22 wherein the first or second group of cells is obtained from a transgenic animal, whose phenotype is not claimed. The claim does not require that the transgenic animal be of a specific phenotype, but only that the cells are derived from a transgenic animal. Nakajima make clear that cells are readily obtainable that express either "wildtype" or "HERG with a mutation." The Examiner has offered no scientific reasoning as to why transgenic cells could not also be altered by transformation to express a wildtype or mutant HERG. It is thus submitted that the claims as amended are enabled.

In view of the foregoing amendments and remarks, it is respectfully submitted that the claims as amended satisfy the provisions of 35 U.S.C. 112, first paragraph, and withdrawal of this rejection is requested.

35 U.S.C. 112 indefiniteness rejections

The claims were also rejected under 35 U.S.C. § 112, second paragraph, as indefinite for reciting the phrases "bathing solution," and "more similar." The claims have been amended to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

In view of the foregoing amendments and remarks, it is respectfully submitted that the claims as amended satisfy the provisions of 35 U.S.C. 112, second paragraph and withdrawal of this ground of rejection is requested.

35 U.S.C. 103 rejections

Claims 22-24 were also rejected under 35 U.S.C. § 103(a) as unpatentable over Wang et al., Mol. Medicine Today, 1998 (Wang) in view of Nakajima, Cir.Res., 1998 (Nakajima), but only in so far as the claims read on the V614 mutation. The Examiner is of the opinion that Wang teaches that mutations in HERG are linked to LQT2 syndrome, that the mutations act through a loss of function or a dominant-negative mechanism. Nakajima is cited for teaching that the specific mutation A614V in HERG resulted in loss of function of the HERG gene and electrophysiological studies demonstrated that injection of mutant and wildtype HERG cDNA's acted in a dominant-negative manner. The Examiner is thus of the opinion that it would have been obvious to develop a drug screen by measuring K+ current in cells expressing wildtype or mutant HERG since Wang teaches that therapies targeting HERG are proven partially effective and Nakajima provides a method of measuring K+ channel and teaches the 614V mutation.

In response, it is submitted that the 614V mutation was disclosed in the '847 application which predates the disclosure of Nakajima dated August 24, 1998.

In view of the foregoing amendments and remarks, it is respectfully submitted that the claims as amended satisfy the provisions of 35 U.S.C. 103 and withdrawal of this ground of rejection is requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that the claims satisfy the requirements of the patent statutes and reconsideration of the instant application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

RESPECTFULLY SUBMITTED,					
NAME AND REG. NUMBER	Michael J. Moran, Reg. No. 42,013				
SIGNATURE			*DATE*	15 November 2002	
Address	Rothwell, Figg, Ernst & Manbeck Suite 800, 1425 K Street, N.W.				
City	Washington	*State*	D.C.	*Zip Code*	20005
Country	U.S.A.	*Telephone*	202-783-6040	*Fax*	202-783-6031

Attachments: Marked-up copy of amended claims
References(3)

22. A method to screen for drugs which are useful in treating a person with a mutation in *HERG,* wherein said mutation is one which results in a cysteine at amino acid residue 572, an aspartic acid at amino acid residue 588, a valine at amino acid residue 614, an alanine at amino acid residue 630 or [a mutation shown in Table 7] a lysine at amino acid residue 29, said method comprising:

a) placing a first set of cells expressing HERG with a mutation, wherein said mutation is a cysteine at amino acid residue 572, an aspartic acid at amino acid residue 588, a valine at amino acid residue 614, an alanine at amino acid residue 630 or a leucine at amino acid residue 29 [, or a mutation shown in Table 7], into a bathing solution [to measure]suitable for measuring a first induced K^+ current;

b) measuring said first induced K^+ current;

c) placing a second set of cells expressing wild-type HERG into a bathing solution [to measure]suitable for measuring a second induced K^+ current;

d) measuring said second induced K^+ current;

e) adding a drug to the bathing solution of step (a);

f) measuring a third induced K^+ current of cells in step (e); and

g) determining whether the third induced K^+ current is [more similar to] closer in value to the second induced K^+ current than is the first induced K^+ current, wherein drugs resulting in a third induced K^+ current which is closer in value to the second induced K^+ current than is the first induced K^+ current are useful in treating said persons.

23. The method of claim 22 wherein cells of said first set of cells are transfected with a mutant *HERG* wherein said mutant *HERG* encodes a HERG protein with a cysteine at amino acid residue 572, an aspartic acid at amino acid residue 588, a valine at amino acid residue 614, an alanine at amino acid residue 630 or [a mutation shown in Table 7] a leucine at amino acid residue 29.